Staff Background Paper
for November 30, 1999 Meeting of
SAB/SAP Joint Subcommittee on
Data from Human Subjects

It is the objective of this second meeting of the SAB/SAP Joint Subcommittee on Data from Human Subjects to discuss the issues in the subcommittee's original charge, with particular attention to those which have divided the subcommittee in its deliberations since its first meeting last December, and with a clear focus on the practical questions confronting the pesticide program as it implements the Food Quality Protection Act of 1996.

Since the first meeting of this panel last year many aspects of the context of the discussion haven't changed. Unsolicited reports of research with human subjects continue to be submitted to the Office of Pesticide Programs, including half a dozen new systemic toxicity studies to establish a human NOAEL. The Agency's policy continues as it was first articulated in July 1998: we will not rely on these studies to support final decisions under the Food Quality Protection Act until a policy is in place that can ensure they meet the highest scientific and ethical standards. We have delayed development of that policy, so that we could have the benefit of the advice of the SAB/SAP panel.

During the past year various offices in EPA have continued to perform or to support many kinds of research with human subjects, with the oversight and subject protection required by the Common Rule. And required studies involving research with human studies have also continued to be submitted to the Agency, including studies of pesticide applicator and field worker exposure performed consistent with published EPA test guidelines, which include requirements similar to the Common Rule.

We want to make you aware of several relevant developments that have occurred since the first meeting of the panel. The Agency has made many of the tolerance reassessment decisions required of it under the FQPA, and met the statutory deadline for the first third of tolerance reassessments by this past August. The Agency has reconsidered some of the earlier human studies it has accepted in the past, and found them unacceptable by contemporary scientific standards.

Although one of the outcomes of this discussion is expected to be a refinement of Agency-wide policy on research with human subjects, the immediate focus of our concern continues to be with pesticides. This is because industry interest in performing pesticide research with human subjects has apparently increased.

New Legal Requirements

Among the many requirements of the Food Quality Protection Act (FQPA) are these affecting risk assessment and protection of children:

- FQPA requires us to reassess over 9,000 current pesticide residue tolerances by 2006. A 'tolerance" is a regulation defining the allowable amount of a pesticide on a food.

- FQPA requires us to consider together the cumulative risks of all pesticides with a common mechanism of action–in effect, to assess the risk of entire classes of pesticides at once. This is in contrast to the past practice of assessing exposures to only one pesticide at a time.

- FQPA calls for use of an additional tenfold safety factor in Agency risk assessments, to increase protection for infants and children, unless reliable data support the use of a different factor.

- FQPA requires EPA to address the 'worst first'–i.e., to begin with the pesticides that are likely to be riskiest. Because of their generally high toxicity and widespread use, the organophosphates and carbamates are under active review, with decisions required soon. Both of these pesticide classes include cholinesterase inhibitors with some history of human testing.

Significance of Human Testing for EPA Risk Assessment

The reference dose (RfD) for a pesticide--the 'safe' daily dose–is calculated by dividing the 'no observed adverse effect level' or NOAEL from the appropriate study (usually the most sensitive study in the most sensitive species) by a series of uncertainty factors. When we calculate an RfD from the endpoint of an animal study, we usually apply a tenfold uncertainty factor to accommodate variability between the test species and humans, unless we have data which support a different factor. When we calculate a reference dose from the endpoint of a human study, we drop this interspecies factor of ten.

So while the FQPA calls for an ***additional*** tenfold safety factor to protect children, changing from an animal end point to a human end point for the RfD calculation could ***eliminate*** the 10-fold interspecies factor from the calculation. It is unusual for the actual numerical value of the NOAEL to be identical in human and animal studies, but using human data generally tends to raise the 'safe dose,' even as the additional FQPA factor works to lower it. All else being equal, a higher 'safe dose' means that more use of a pesticide can be permitted, and a lower 'safe dose' can lead to regulatory reductions on permissible use. Thus the FQPA requirement for an additional uncertainty factor may have unintentionally created an incentive to test pesticides in humans.

Human testing with pesticides is clearly on the increase. After receiving only a handful of similar studies during the preceding ten years, since passage of FQPA the Office of Pesticide Programs has received fourteen unsolicited new studies on ten different pesticides, all intended to define a human systemic NOAEL. We expect to receive more. These studies raise difficult scientific and ethical questions we are not yet able to answer, and we are deeply concerned about them.

Others are concerned as well. In July 1998 the Environmental Working Group published a report that focused public attention on human studies–studies which expose human volunteers to cholinesterase-inhibiting pesticides to find a 'no observed adverse effect level' or NOAEL which can be used to calculate a reference dose. In the past year and a half many others have weighed in, arguing both for and against consideration of human studies in our reassessments of tolerances under FQPA.

Agency Concerns

In this arena of controversy, the Agency has several abiding concerns:

- We want to rely on data meeting the highest scientific and ethical standards--the most appropriate and the most reliable available, able to support the most accurate assessments of potential risk. In the case of pesticides, EPA has the authority to specify what tests are required and how they should be performed. We do this through "test guidelines", developed in collaboration with other regulatory agencies here and abroad, and subjected to rigorous peer review before adoption. We have never defined guidelines for testing pesticide effects or establishing NOAELs in human subjects. We do not require such studies; we do not encourage them; we do not believe them to be necessary to good risk assessments. Nevertheless the argument is made that human studies are more appropriate to an assessment of human health risk than animal studies, that they are more reliable than animal studies, and that they support more accurate assessments of potential risk.

- We want a policy that applies protections like those in the Common Rule consistently and fairly to all human research supported or considered by the Agency, so that all human research EPA supports or considers meets a consistent standard.

- We want a policy that sets clear standards for ethical and scientific quality and acceptability of human studies submitted for our consideration. These standards must be subjected to peer review and public comment.

- We want a policy that recognizes the wide range of human research that EPA may perform, require, or consider, including incident followup, epidemiological studies, patch tests for irritancy or sensitization, exposure studies of people performing their normal activities, studies of pharmacodynamics or metabolism, and testing to establish a NOAEL. When it is appropriate, we want to distinguish among these different kinds of human research. While some general standards may apply to all of them, specific criteria for acceptability may well vary, and we are asking for your help to define those distinctions and specific criteria.

- We realize that ethical standards have changed over time, and that many studies were performed before current standards were in place. We ask for your help in applying contemporary standards to older data. We must also ensure that any studies we use which were performed in other countries can meet the ethical standards of our country.

Future Policy Development

We will incorporate your advice into our policy development, and will make our policy available for public review and comment. We will respect the role of other Agencies with related missions and concerns–especially the Department of Health and Human Services, which we rely on as the federal lead agency for this issue. We recognize that whatever policy we develop today will necessarily be subject to future review and modification as standards evolve.

Human Systemic NOAEL Studies Submitted to OPP Since FQPA

Chemical/Class	Exposure	Citation
DDVP Organophosphate	Oral	44248801 Gledhill, A. (1997) Dichlorvos: A Single Blind, Placebo Controlled Randomised Study to Investigate the Effects of Multiple Oral Dosing on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers: Lab Project Number: CTL/P/5392: XH6063. Unpublished study prepared by Zeneca Central Toxicology Lab. 52 p.
	Oral	44248802 Gledhill, A. (1997) Dichlorvos: A Study to Investigate the Effect of a Single Oral Dose on Erythrocyte Cholinesterase Inhibition in Healthy Male Volunteers: Lab Project Number: CTL/P/5393: XH6064. Unpublished study prepared by Zeneca Central Toxicology Lab. 44 p.
	Oral	44308001 Manley, A. (1997) Metrifonate (MTF)/Dichlorvos (DDVP): Position Document on Long Term Administration in Humans: Lab Project Number: AM/001. Unpublished study prepared by Amvac Chemical Corp. 146 p.
	Oral	44317901 Gledhill, A. (1997) Dichlorvos: A Study to Investigate Erythrocyte Cholinesterase Inhibition Following Oral Administration to Healthy Male Volunteers: Lab Project Number: XH5170: CTL/P/5251. Unpublished study prepared by Central Toxicology Lab. 66 p.
		44416201 Gledhill, A. (1997) Dichlorvos: A Study to Investigate Erythrocyte Cholinestrase Inhibition Following Oral Administration to Healthy Male Volunteers: Lab Project Number: XH5170: Y09341: C05743. Unpublished study prepared by Zeneca Central Toxicology Lab. 104 p.
RH-7988 ?	Oral	44350534 Sanderson, J.; Dickson, J.; Hastings, L. (1997) A Randomized Double Blind Ascending Dose Study to Determine the Safety and Tolerability of RH-7988 and to Establish a No Adverse Effect Level in Healthy Male Volunteers: Final Report: Lab Project Number: 96P-096: 96 RC-096: 14334. Unpublished study prepared by Inveresk Clinical Research. 519 p.
Amitraz Non-cholinergic Neurotoxicant	Dermal	44639401 Langford, H. (1998) Amitraz (Code AE B049974): Human Volunteer Double-Blind Dermal Tolerance Study: Lab Project Number: C00350: TOX 97228: RD 197/21690. Unpublished study prepared by Simbec Research Ltd. 243 p.
Cyfluthrin Pyrethroid	Inhalation	44657601 Ruddy, K.; Mair, S.; McInally, K. (1997) Safety and Tolerability Study of FCR 1272 0.04 AE in Healthy Volunteers: Lab Project Number: 11590: ICR 011337. Unpublished study prepared by Inveresk Clinical Research. 285 p.
Methomyl Carbamate	Oral	44721401 McFarlane, P.; Sanderson, J.; Freestone, S. (1998) A Randomised Double Blind Ascending Oral Dose Study with Methomyl to Establish a No Adverse Effect Level: Lab Project Number: HLO-1998-00969: 11739: ICR 012456. Unpublished study prepared by Inveresk Clinical Research. 468 p. Relates to L0000306.

Chemical/Class	Exposure	Citation
Azinphos-methyl Organophosphate	Oral	44786901 McFarlane, P.; Freestone, S. (1998) ICR 013219: A Randomised Double Blind Ascending Single Oral Dose Study with Azinphos-Methyl to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity: Lab Project Numbers: 0131219, 108963. Unpublished study prepared by Inveresk Research. 765 p.
Chlorpyrifos Organophosphate	Oral	44811002 Kisicki, J.; Wilkinson Seip, C.; Combs, M. (1999) A Rising Dose Toxicology Study to Determine the No-Observable-Effect-Levels (NOEL) for Erythrocyte Acetylcholinesterase (AChE) Inhibition and Cholinergic Signs and Symptoms of Chlorpyrifos at Three Dose Levels: Lab Project Number: 21438: DR# K-044793-284: 432-01. Unpublished study prepared by MDS Harris. 578 p.
Phosmet Organophosphate	Oral	44851001 Freestone, S.; Mair, S.; McFarlane, P. (1999) A Randomised, Double Blind, Ascending Single Oral Dose Study with Phosmet to Determine the No Effect Level on Plasma and RBC Cholinesterase Activity: Lab Project Number: ICR 013533: 17367. Unpublished study prepared by Inveresk Clinical Research Limited. 666 p.
Oxamyl Carbamate	Oral	44912301 McFarlane, P.; Freestone, S. (1999) A Randomised Double Blind Ascending Oral Dose Study with Oxamyl: Lab Project Number: ICR 012765: 12245: HLO-1998-01505. Unpublished study prepared by Inveresk Clinical Research. 624 p.
ZA 1296 Triketone	Dermal	44920803 Hall, M. (1998) ZA1296: Investigation of Systemic Exposure Following a Single Dermal Application of Spray Formulations to Healthy Male Volunteers: Lab Project Number: CTL/P/5921: QH0020: ICR 012571. Unpublished study prepared by Zeneca Central Toxicology Laboratory. 664 p.